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Rule-out of non-ST elevation myocardial infarction by five point of care cardiac troponin assays according to the 0 h/3 h algorithm of the European Society of Cardiology

Suh, Durie ; Keller, Dagmar I ; Hof, Danielle ; von Eckardstein, Arnold ; Gawinecka, Joanna

Abstract: BACKGROUND Point of care (POC) assays for cardiac troponins I or T (cTnI or cTnT) may accelerate the diagnosis of patients with suspected acute coronary syndrome (ACS). However, their clinical utility according to the 0 h/3 h algorithm recommended by the European Society of Cardiology (ESC) for non-ST elevation myocardial infarction (NSTEMI) is unknown. METHODS Blood samples from 90 patients with suspected ACS were obtained at hospital admission and 3 h later. Concentrations of cTn were determined using five POC assays (AQT90 FLEX cTnI and cTnT; PATHFAST™ cTnI; Stratus CS 200 cTnI; and Triage MeterPro cTnI) and two guideline-acceptable high-sensitivity (hs) immunoassays. RESULTS For the diagnosis of NSTEMI (n=15), AUCs for Abbott hs-cTnI and Roche hs-cTnT were 0.86 [95% confidence interval (CI), 0.75-0.96] and 0.88 (95% CI, 0.80-0.95), respectively, at admission, and 0.96 and 0.94, respectively, 3 h later. With the 99th percentile cutoff, their sensitivities were 62% and 92%, respectively, at admission, and 77% and 100%, respectively, 3 h later. The PATHFAST™ cTnI assay showed AUCs of 0.90 (95% CI, 0.82-0.97) and 0.94 (95% CI, 0.89-1.00), respectively, and sensitivities of 67% and 75% at admission and 3 h later, respectively. The other cTn POC assays had AUCs of 0.71 (95% CI, 0.53-0.89) to 0.84 (95% CI, 0.71-0.96) and 0.86 (95% CI, 0.72-0.99) to 0.87 (95% CI, 0.75-0.99) and sensitivities of 39%-50% and 62%-77% at admission and 3 h later, respectively. CONCLUSIONS PATHFAST™ cTnI assay proved itself as comparable to ESC-guideline acceptable hs-cTn assays. The lower sensitivity of the other POC assays limits their clinical utility and would require longer follow-up monitoring of patients for the safe NSTEMI rule-out.

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Abstract

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Conclusions: PATHFAST™ cTnI assay proved itself as comparable to ESC-guideline acceptable hs-cTn assays. The lower sensitivity of the other POC assays limits their clinical utility and would require longer follow-up monitoring of patients for the safe NSTEMI rule-out.

Keywords: acute myocardial infarction; point of care (POC) troponin.

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Introduction

The measurement of cardiac troponins I or T (cTnI or cTnT) complements the clinical assessment and resting 12-lead ECG in the diagnosis, risk stratification and therapy of patients with acute coronary syndrome (ACS). Patients showing ST elevation on electrocardiography (ECG) are directly referred to the catheterization laboratory without awaiting results of cardiac troponin tests [1]. In ACS patients without ST elevation (NSTE-ACS), cTn measurement is indispensable to distinguish high-risk patients with non-ST elevation myocardial infarction (NSTEMI), who require rapid invasive intervention, from low-risk patients with unstable angina pectoris [2]. For NSTE-ACS patients, time to the clinical decision is strongly influenced by the sensitivity of the cardiac troponin test.

Guideline-acceptable high-sensitivity (hs) assays measure cTn levels representing the 99th percentile of healthy individuals with an imprecision of 10% or less. According to guidelines of the European Society of Cardiology (ESC), cTn levels below the 99th percentile measured by hs-cTn assays in blood samples obtained at admission and 3 h later allow the safe rule out of NSTEMI. Conventional assays with an imprecision ranging between 10% and 20% are considered as clinically useful but need follow-up time of 6 h to rule out NSTEMI [2, 3].

Due to their short turnaround time, point-of-care (POC) assays have the potential to accelerate the management of NSTE-ACS patients in the emergency department. However, POC cTn assays have not yet been evaluated as thoroughly as automated hs-cTn assays performed in central laboratories, which form the basis of current guidelines. As yet, most of them have been assigned to the scorecard categories (guideline acceptable, clinically useful or not acceptable) based on the manufacturers' self-declarations on imprecision and 99th percentiles rather than on the basis of publicly available reports of clinical studies [4]. Therefore, in a series of whole blood samples freshly obtained from

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90 patients with suspected ACS, we compared the analytical and diagnostic performance of five point of care (POC) assays and two guideline-compatible central laboratory assays for cTnI or TnT according to the 0 h/3 h algorithm recommended by ESC for the NSTEMI management.

Materials and methods

Study population

The study was performed at the University Hospital Zurich (USZ) between January and December 2016 upon approval of the Cantonal Ethic Committee Zurich (KEK-ZH-Nr. 2016-00378). Patients who presented themselves on working days between 8:00 am and 6:00 pm with clinical symptoms suggestive for cardiac ischemia were recruited at the emergency department and, after providing the informed consent, enrolled into the study. All diagnostic procedures including ECG recordings and clinical assessment were performed according to the standardized procedures in patients presenting with chest pain at the emergency department. Venous blood samples anticoagulated either with Li-heparinate or K-EDTA for the study purposes were collected together with diagnostic specimens at hospital admission and again 3 h later. For some patients, blood samples were only available from the time point of admission. The detailed characteristics of the patients are provided in Table 1. All final diagnoses were adjudicated by an experienced cardiologist, and all ACS cases were confirmed through coronary angiography.

Table 1: Characteristics of study population.

Study population (n = 90)	
Age, mean ± SD, years	60 ± 17
Male sex	60 (67%)
Risk factors	
Hypertension	48 (53%)
Diabetes mellitus	17 (19%)
Current smoking	25 (28%)
Hypercholesterolemia	31 (34%)
Medical history	
Coronary heart disease	28 (31%)
Previous myocardial infarction	14 (16%)
Previous revascularization or bypass surgery	11 (12%)
Chronic kidney disease (eGFR < 60)	18 (20%)
Medication at the hospital admission	
Aspirin	31 (34%)
β-Blocker	18 (20%)
ACE inhibitor	14 (16%)
ATII antagonists	22 (24%)
Calcium antagonists	12 (13%)
Diuretics	19 (21%)
Nitrates	4 (4%)
Statin	25 (28%)
Anti-platelet agents	6 (7%)
ECG findings	
ACS specific	18 (20%)
Other changes	30 (33%)
Normal	42 (47%)
Chest pain onset	
> 3 h	79 (88%)
> 6 h	63 (70%)
> 24 h	34 (38%)
Final diagnosis	
STEMI	2 (2%)
NSTEMI	15 (17%)
Unstable angina pectoris	7 (8%)
Other cardiac	12 (13%)
Non-cardiac	54 (60%)

Selection of POCTs for cTn

We approached and asked six manufacturers or sale representatives of seven POC assays for cTnI or cTnT. Finally, Alere with Triage MeterPro with Next Generation TnI, Radiometer with AQT90 FLEX for both cTnI and cTnT, Axonlab with PATHFAST™ Immunoanalyzer from LSI Medience Corporation and Siemens with Stratus CS 200 agreed to join the study and provided POC devices, tests and control materials free of charge.

cTn assays

Fresh K-EDTA whole blood samples were analyzed on the Triage MeterPro with Next Generation TnI (Alere, Waltham, MA, USA) for cTnI, whereas fresh Li-heparinate whole blood samples were analyzed on PATHFAST™ Immunoanalyzer (LSI Medience Corporation, Tokyo, Japan) for cTnI and on AQT90 FLEX (Radiometer, Copenhagen, Denmark) for both cTnI and cTnT. The blood collection tube could be place directly in Stratus C2 200 (Siemens, Erlangen, Germany) with on board centrifugation (2.5 mL of whole blood required). However, due to the limited sample volume available for the study, whole blood samples were processed in the external centrifuge, and one plasma aliquot (400 µL) was analyzed for the cTnI on Stratus CS 200. Remaining plasma aliquots were stored frozen at –80 °C for further analysis for hs-cTnI on Architect i2000SR (Abbott Diagnostics Lake Bluff, IL, USA). The hs-TnT assay was performed on Cobas 8000 e602 modular analyzer (Roche Diagnostics, Rotkreuz, Switzerland) using diagnostic samples. Table 2 provides detailed characteristics of the cTn assays as stated by their manufacturers. All reagents, tests and control materials were stored according to the manufacturer's instruction.

For POC assays, quality control (QC) material provided by the manufacturers was measured before measurement of the first patient's blood samples, and results were considered valid for 24 h. The imprecision profiles were generated by measuring patient's blood samples five times, calculating mean concentrations, and CV%.

Statistical data analysis

Statistical analysis was performed using SPSS 23.0 (IBM, USA) and Analyse-it Method evaluation 4.65.3 (Microsoft, USA). The proportional variance fit model was applied to calculate imprecision (CV%)

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Table 2: Characteristics of the cTn assays as defined by the manufacturer.

System	POC					Core-lab analyzer	
Manufacturer	Alere	Radiometer		LSI Medience Corporation	Siemens	Roche	Abbott
Name	Triage MeterPro mit next generation TnI	AQT90 FLEX		PATHFAST™	Stratus CS 200	Elecsys Cobas 8000	Architect i2000SR
Troponin	cTnI	cTnT	cTnI	cTnI	cTnI	hs-cTnT	hs-cTnI
Measuring range, ng/L	10–10,000	10–25,000	10–50,000	1–50,000	30–50,000	3–10,000	10–50,000
99th percentile, ng/L	20	17	23	20	70	14	26
CV (%) at 99th percentile	<17	15	12	5.2	<10	<10	4
CV = 10% at concentration, ng/L	37	26	27	3.1	60	13	4.7
Specimen	EDTA whole blood or plasma	Heparin and EDTA whole blood or plasma		Heparin and EDTA whole blood or plasma	Heparin whole blood or plasma	Serum, heparin and EDTA plasma	Serum, heparin and EDTA plasma
Sample volume	250 µL	2 mL		100 µL	200 µL plasma or 2–2.5 mL whole blood	50 µL	210 µL

at 99th percentiles reported by each manufacturer. The following number of samples was included in the model: 26, 31, 28, 41 and 30 for cTn assay on Triage MeterPro, TnT AQT90 FLEX, TnI AQT90 FLEX, PATHFAST™ and Stratus CS 200, respectively. The receiver operating characteristic (ROC) curves were applied to measure diagnostic performance of cTn assays. To compare area under curves (AUCs), nonparametric z test was applied.

Evaluation of user-friendliness

Two independent users assessed the practical utility of the POC systems. The following aspects were assessed: (a) time factors: preanalytical and analytical time, and required training time; (b) stability and storage of QC material; (c) test stability; (d) operation facilities: sample preparation and volume, instrument design, hygiene, cleaning and maintenance.

Results

Study population

Ninety patients were enrolled in the study. Fifteen patients had NSTEMI, two STEMI and seven unstable angina pectoris. In 12 patients, chest pain had other cardiac causes, such as cardiac decompensation or pericarditis. In 54 patients, chest pain was not related to any cardiac etiology but caused by musculoskeletal and dyspeptic complaints or psychiatric problems in most cases. In 74 patients (82%), at least one cardiovascular risk factor was present, and 28 patients (31%) had a history of coronary artery disease. The duration of chest pain at the hospital admission was longer than 6 h in 63 patients (70%).

The analytical quality of the POC assays

The imprecision and accuracy of the POC assays were assessed by single measurements of QC material provided by the respective manufacturer at two levels – except Triage MeterPro where only one level was provided (Table 3 and Supplemental Figure 1). The imprecision of cTnT on AQT90 FLEX as well as cTnI on Triage MeterPro, Stratus CS 200 and AQT90 FLEX level 2 corresponded to the manufacturer's specifications. The imprecision of AQT90 FLEX cTnI on level 1 was slightly higher than the manufacturer's quality specification. For PATHFAST™, the CV's were twice as high as claimed by the manufacturer. Measured mean cTn concentrations differed significantly from target cTn concentrations provided by the manufacturers for the Triage MeterPro (34%), PATHFAST™ (11% for level 1 and –7.6% for level 2) and AQT90 FLEX cTnI level 1 (–15%).

The imprecision profiles with proportional variance fit model were used to assess both the imprecision (CV%) at the 99th percentile stated by the manufacturer and the functional assay sensitivity (FAS) defined as the lowest cTn concentration measured with an imprecision of 10% (Table 4 and Figure 1). The manufacturer of the PATHFAST™ cTnI assay claims the imprecision of 5% at the 99th percentile

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Table 3: Analytical quality of the cTn POC assays using QC material provided by manufacturers.

POC System	Control material	Target cTn concentration, ng/L	Measured mean cTn concentration, ng/L	Bias, %	CV%
PATHFAST™	QC level 1	73	81	11	7.7
	QC level 2	1370	1266	−7.6	8.0
Stratus CS 200	QC level 2	942	944	0.2	2.9
	QC level 3	3890	3977	2.2	4.5
AQT90 FLEX cTnI	MC1	36	31	−15	11
	MC2	1120	1127	0.6	3.7
AQT90 FLEX cTnT	TnT1	56	56	0.8	5.1
	TnT2	853	884	3.6	2.8
Triage MeterPro	Triage total level 1	40	54	34	13

that corresponds to 20 ng/L. However, we measured cTnI concentrations of 20 and 24 ng/L with imprecision of 11.5% and 10%, respectively. Both the imprecision at the claimed 99th percentile and FAS of Stratus CS 200 cTnI corresponded well to the manufacturer's specifications (9.2% observed vs. <10% claimed and 64 ng/L observed vs. 60 ng/L claimed, respectively). For the TnI assay on AQT90 FLEX, both imprecision at the 99th percentile and FAS were even lower than the manufacturer's specification (7.4% observed vs. 12% claimed and 16 ng/L observed vs. 27 ng/L claimed, respectively). For the cTnT assay on AQT90 FLEX, the claimed and measured imprecision at the 99th percentile (17 ng/L) was practically identical (15% vs. 16%), whereas the FAS was higher than claimed (31 vs. 26 ng/L). The Triage MeterPro cTnI assay showed an extremely high imprecision at the 99th percentile (20 ng/L) of 40% (claimed <17%). The imprecision of 10% was only reached at cTnI concentrations as high as 840 ng/L.

Diagnostic performance of POC assays in the diagnosis of NSTEMI

ROC curve analyses were applied to estimate the diagnostic performance of the cTn assays. For the calculations, patients with final diagnosis of NSTEMI were defined as cases, and patients with either other, non-cardiac chest pain or unstable angina pectoris were defined as controls. Moreover, from these patients, blood samples had to be available at the hospital admission and 3 h later. The reference assays, Abbott hs-cTnI and Roche hs-cTnT had AUCs of 0.86 [95% confidence interval (CI), 0.75–0.96] and 0.88 (95% CI, 0.80–0.95), respectively, at hospital admission, and of 0.96 (95% CI, 0.92–1.00) and 0.94 (95% CI, 0.88–0.99), respectively, 3 h later. At hospital admission, cTnT assay on AQT90 FLEX reached AUC of 0.74 (95% CI, 0.59–0.89), and cTnI assays on AQT90 FLEX, PATHFAST™ and Stratus CS 200 reached AUCs of 0.84 (95% CI, 0.71–0.96), 0.90 (95% CI, 0.82–0.97) and 0.76 (95% CI, 0.62–0.90), respectively, which were not significantly different from that of the Abbott hs-cTnI assay. By contrast, Triage MetePro cTnI assay with AUCs of 0.71 (95% CI, 0.53–0.89) performed significantly worse than the hs-cTnI assay. The performances of cTnI assays on Triage Meter Pro, AQT90 FLEX and PATHFAST™ were statistically comparable, whereas Stratus CS 200 cTnI and AQT90 FLEX TnT assays were worse than Roche hs-cTnT assay at the time point of the hospital admission (Table 5, Figure 2 and Supplemental Table 1). Significant increases in AUC for measurements of samples obtained 3 h postadmission were

Table 4: Imprecision and functional assay sensitivity of the cTn POC assays derived from measurement of patients' whole blood samples.

	PATHFAST™		Stratus CS 200		AQT90 FLEX cTnI		AQT90 FLEX cTnT		Triage MeterPro	
	Claimed	Measured	Claimed	Measured	Claimed	Measured	Claimed	Measured	Claimed	Measured
99th percentile, ng/L[a]	20	–	70	–	23	–	17		20	–
CV (%) at 99th percentile	5	11.5	<10	9.2	12	7.4	15	16	<17	40
Functional assay sensitivity (FAS)[b], ng/L	3	24	60	64	27	16	26	31	37	840
Classification	Guideline acceptable	Clinically usable	Guideline acceptable	Guideline acceptable	Clinically usable	Guideline acceptable	–	Clinically usable	Clinically usable	Not acceptable

[a]Defined by the manufacturer. [b]Defined as the concentration which was measured with CV of 10%.

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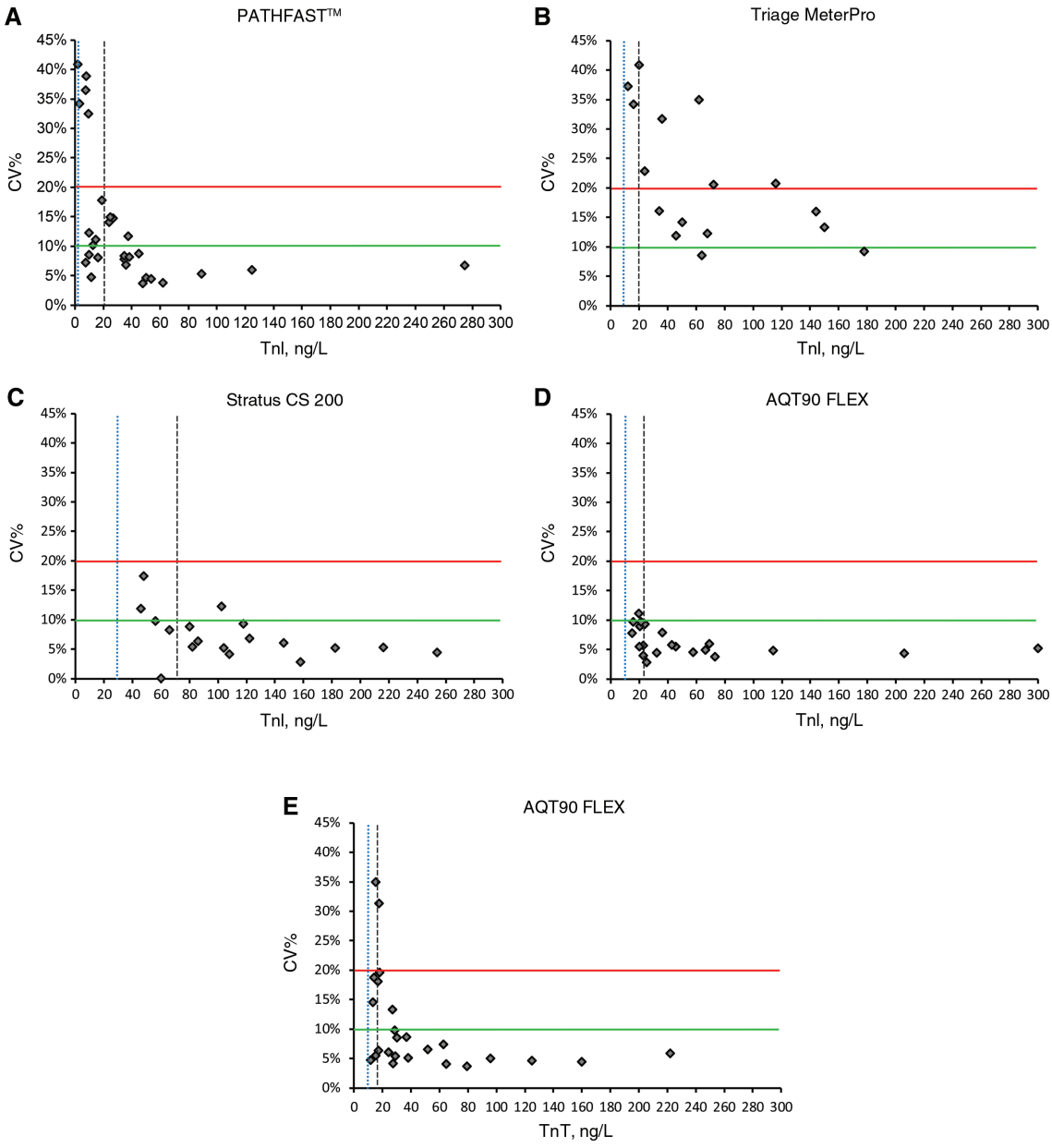

Figure 1: Imprecision profiles of POC assays.
Blue dotted line – limit of detection; black dashed line – 99th percentile of the healthy population; green line – imprecision of 10% (guideline acceptable); red line – imprecision of 20% (clinically usable).

observed for both hs-cTn and AQT90 FLEX cTnT assays. In turn, statistical significance for the increase in AUC was marginally missed for cTnI assays on Triage MeterPro and PATHFAST™ (Table 5, Figure 2 and Supplemental Table 2). There were no statistical differences in AUC between cTnI assays on Stratus CS 200 and AQT90 FLEX. Furthermore, 3 h postadmission, all POC assays performed equally as the hs-cTn assays (Supplemental Table 1).

At the time point of the hospital admission, the PATHFAST™ cTnI assay showed a similar performance as the AQT90 FLEX cTnI assay but was superior to the cTnI assays Triage MeterPro and Stratus CS 200 as well as to the AQT90 FLEX cTnT assay. Three-hour postadmission, there was no statistical difference between PATHFAST™ cTnI assay and other POC assays (Supplemental Table 3).

At the 99th percentile cutoff concentration claimed by the manufacturers and at the time point of a patient's admission to the emergency department, the referent Abbott hs-cTnI and Roche hs-cTnT assays had sensitivities of 62% (95% CI, 35–82%) and 92% (95% CI, 67–99%), respectively, and negative predictive values (NPVs) of 92%

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Table 5: Diagnostic performance of cTn assays in the diagnosis of myocardial infarction.

Assay	Cutoff, ng/L	n[a]	0 h					3 h				
			AUC (95% CI)	Sensitivity[b] (95% CI)	Specificity[b] (95% CI)	NPV[c] (95% CI)	PPV[d] (95% CI)	AUC (95% CI)	Sensitivity[b] (95% CI)	Specificity[b] (95% CI)	NPV[c] (95% CI)	PPV[d] (95% CI)
Abbott hs-cTnI	26	13/68	0.86 (0.75–0.96)	62% (36%–82%)	88% (79%–94%)	92% (86%–96%)	50% (31%–69%)	0.96 (0.92–1.00)	77% (50%–92%)	87% (77%–93%)	95% (88%–98%)	53% (36%–69%)
Roche hs-cTnT	14	13/68	0.88 (0.80–0.95)	92% (67%–99%)	71% (59%–80%)	98% (88%–100%)	38% (29%–47%)	0.94 (0.88–0.99)	100% (77%–100%)	72% (60%–81%)	100% –	41% (32%–50%)
Triage MeterPro	20	10/41	0.71 (0.53–0.89)	50% (24%–76%)	93% (81%–98%)	88% (80%–93%)	63% (32%–85%)	0.86 (0.72–1.00)	70% (40%–89%)	88% (75%–95%)	92% (82%–97%)	58% (36%–78%)
AQT90 FLEX cTnI	23	13/63	0.84 (0.71–0.96)	46% (23%–71%)	94% (85%–98%)	89% (84%–93%)	60% (33%–82%)	0.86 (0.72–0.99)	69% (42%–87%)	92% (83%–97%)	94% (87%–97%)	64% (42%–82%)
PATHFAST™	20	12/63	0.90 (0.82–0.97)	67% (39%–86%)	91% (81%–96%)	93% (86%–97%)	57% (36%–76%)	0.94 (0.89–1.00)	75% (47%–91%)	87% (77%–93%)	95% (87%–98%)	53% (35%–70%)
Stratus CS 200	70	13/63	0.76 (0.62–0.90)	39% (18%–65%)	92% (83%–97%)	88% (82%–92%)	50% (25%–75%)	0.86 (0.73–0.99)	77% (50%–92%)	92% (83%–97%)	95% (88%–98%)	67% (45%–83%)
AQT90 FLEX cTnT	17	13/63	0.74 (0.59–0.89)	46% (23%–71%)	87% (77%–93%)	89% (83%–93%)	43% (24%–64%)	0.87 (0.75–0.99)	62% (36%–82%)	86% (75%–92%)	92% (84%–96%)	47% (30%–65%)

[a]NSTEMI/controls. [b]Sensitivity and specificity were calculated at the cutoff. [c]Negative predictive value. [d]Positive predictive value.

(95% CI, 86–96%) and 98% (95% CI, 88–100%), respectively. At this time point, PATHFAST™ cTnI assay had the highest sensitivity of 67% (95% CI, 39–86%) and NPV of 93% (95% CI, 86–97%) of all POC assays. In general, sensitivities of POC were statistically equal to the sensitivity of Abbott hs-cTnI assay and with the exception for PATHFAST™ cTnI assay inferior to the sensitivity of Roche hs-cTnT assay (data not shown). At the time point of the second cTn measurement 3 h postadmission, the referent Abbott hs-cTnI and Roche hs-cTnT assays had sensitivities of 77% (95% CI, 50–92%) and 100% (95% CI, 77–100%), respectively, and NPVs of 95% (95% CI, 88–98%) and 100%, respectively. Stratus CS 200 cTnI assay had the same sensitivity and NPV of 77% (95% CI, 50–92%) and 95% (95% CI, 88–98%), respectively, as the Abbott hs-cTnI assay. The other POC assays had lower sensitivities ranging from 62% (95% CI, 36–82%) for the AQT90 FLEX cTnT assay to 75% (95% CI, 47–91%) for the PATHFAST™ cTnI assay. Three-hour postadmission, NPVs of the POC cTn assays ranged between 92% and 95% and, hence, were within the range of the Abbott hs-cTnI assay (Table 5).

Practicability

Detailed information on user friendliness is provided in Supplemental Table 4. The main advantage of the Triage MeterPro is its very small, portable size. The QC material is provided in the practical single-use ampules that can be thawed directly before use. PATHFAST™ allows simulations measurements of up to six samples (patient's blood and QC). Both Triage MeterPro and PATHFAST™ require pipetting of the blood sample into the test cartridge, risking measurement errors by non-proper mixing of blood samples before pipetting. This sample handling also exposes users to accidental contact with blood. Because blood collection tubes can be placed directly into the device, AQT90 FLEX does not require any blood sample preparation. Although 2 mL of blood is needed in the collection tube, actually only 15–20 µL is used for the analysis. The AQT90 FLEX test cartridges containing 16 tests that can be stored on board for up to 2 weeks; therefore, it allows immediate sample measurement. Moreover, AQT90 FLEX is the only tested device, which does not impose any contact with blood, reagents or waste and thereby reduces the exposure to biohazards to the minimum. By analyzing plasma instead of full blood, Stratus CS 200 offers two measurement options: either directly from the blood collection tube, requiring 2.5 mL of whole blood, with on board centrifugation, thereby minimizing exposure to biohazards, or precentrifuged plasma in the test cup.

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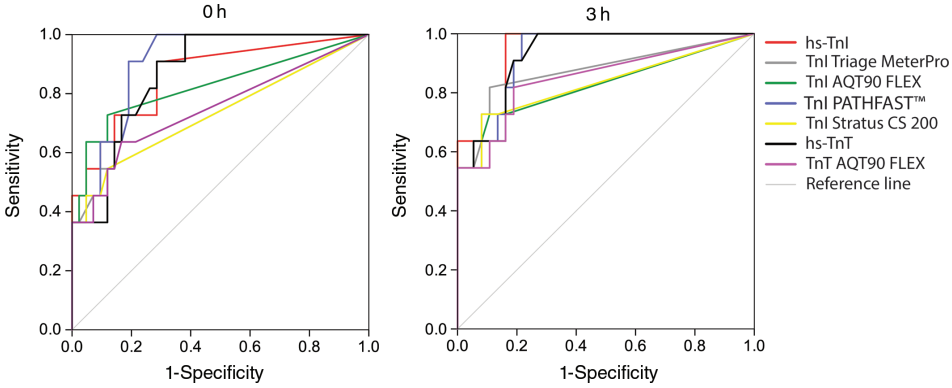

Figure 2: ROC curves of cTn assays at the hospital admission (0 h) and 3 h later.

Moreover, Stratus CS 200 was the largest from the tested POC devices and requires daily system check.

Discussion

The hs-cTn assays performed in central laboratories display high clinical sensitivity and specificity as requested by guidelines for the rule-out and rule-in, respectively, of NSTEMI in patients presenting with chest pain at the emergency department. However, due to blood sample transport and processing, the turnaround time of these hs-cTn assays amounts to 1 h or more [5]. POC assays shorten turnaround times by avoiding the transport of samples to the central laboratory and facilitated sample handling and preparation. Thereby, POC cTn assays have the potential to reduce the length of stay of NSTE-ACS patients in the emergency department and to lower hospital costs [6–8]. In the same time, a randomized controlled trial of POC cTn assays in the emergency department does not find any clinical benefit of cTn testing by POC as compared to the cTn testing in the central laboratory [9]. Nonetheless, potential advantage of POC testing in reducing length of stay of patients with suspected NSTE-ACS in the emergency department can only take place if the POC cTn assays are as sensitive as the hs-cTn assays used in the central laboratories.

For the fast and reliable rule-out, cTn assay must be very precise with an imprecision of <10% CV at the 99th percentile encountered among healthy individuals [10]. In our study 99th percentile cutoffs were provided by the manufacturers of the assays. With this limitation, scorecard requirement for guideline-acceptable hs-cTn assays [4] was achieved by the cTnI assays run either on Stratus CS200 or on AQT90 FLEX. A CV of less than 20% at the 99th percentile is still considered clinically acceptable, as it does not significantly increase the false-positive diagnoses of myocardial infarction [4, 10]. This condition was fulfilled by the PATHFAST™ cTnI assay, which was previously claimed to be guideline acceptable, as well as by the AQT90 FLEX cTnT assay. According to the scorecard criteria [4], the CV of 40% at the clinical decision cutoff classifies the Triage MeterPro cTnT assay as too imprecise for clinical utility. However, this very high imprecision can be partially explained by the device's reporting concentrations only roughly discriminated by 10 ng/L steps. Our finding of higher imprecision of most POC assays and hence lower scorecard classification than claimed by the manufactures has two potential explanations. First, we analyzed whole blood samples rather than accustomed plasma samples. Second, the number of samples might not be sufficient to construct reliable imprecision curves.

A more direct measure of clinical utility of cTn assay is its diagnostic performance. In our study, NSTEMI was ruled out by the finding of two negative test results (0 h, 3 h) of Roche hs-cTnT measurements in the central laboratory. By this study design, the Roche hs-TnT assay was defined as the gold standard, which cannot be surpassed by any other assay. To avoid this bias, we included the Abbott hs-TnI assay, which in several large studies showed the same diagnostic performance as the Roche hs-TnT assay [11, 12]. In our hands, Abbott hs-TnI was considerably less sensitive than Roche hs-TnT both at admission (62% vs. 92%) and 3 h later (77% vs. 100%). Thus, it is more appropriate to compare the data on the diagnostic performance of the POC cTn assays with those of the Abbott hs-cTnI assay rather than with those of the Roche hs-TnT assay.

In our hands, the PATHFAST™ cTnI assay showed the best diagnostic performance of all POC cTn assays, which is in line with the excellent FAS claimed by the manufacturer rather than with the intermediate FAS found by us. The PATHFAST™ cTnI assay performed similarly to the referent Abbott hs-cTnI assay. Therefore, it qualifies as a

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candidate for the application of the 0/1 h algorithm proposed by ESC [2]. Conversely, despite their excellent FAS qualifying them as guideline acceptable assays, the cTnI assays run on Stratus CS 200 and AQT90 FLEX showed very low diagnostic sensitivity at the time point of hospital admission, which however improved markedly, especially for the Stratus CS 200 cTnI assay, when cTnI measurement was repeated 3 h postadmission. One possible reason for the discrepancy between analytical and diagnostic performance of the cTnI assays run on PATHFAST™, Stratus CS 200 and AQT90 FLEX may be caused by the definition of the 99th percentile, which is not standardized and thus can vary due to the demographics and screening methods used to exclude cardiac disease [13]. Therefore, the 99th percentile may be higher than reported for PATHFAST™ but lower than reported for Stratus CS 200 and AQT90 FLEX. The Triage MeterPro cTnI and AQT90 FLEX cTnT assays showed the weakest diagnostic performance at time point of hospital admission.

To our knowledge, our study for the first time had systematically compared the diagnostic performance of five POC cTn assays and two core-lab hs-cTn assays according to the 0/3 h algorithm recommended by ESC guidelines for the management of NSTE-ACS patients [2]. By including the Abbott hsTnI test as a second reference assay, we reduced the bias of the Roche hs-cTnT assay, which was used as the criterion for the rule-out of NSTEMI, and therefore by definition reached 100% sensitivity and NPV in samples obtained 3 h after admission to the hospital. The most substantial weakness of our study is the limited sample size. However, the setting of our study that requires immediate measurement of fresh blood samples using five different assays only allowed to investigate patients hospitalized during regular working days and hours and prevented the large numbers of previous multicentre studies, where plasma samples from biorepositories were analyzed by core-labs [14]. To ensure that our study still provides substantial information on differences in the analytical and clinical performance of the evaluated POC cTn assays, we performed ROC power analysis. For the average number of NSTEMI patients and controls of 12 and 65, respectively, the a priori power was 94%, which is considered as high value of experimental replicability, and therefore our sample size is sufficient to provide reliable results (data not shown). A protocol and study like ours can help to select POC cTn assays, which are likely to reach the analytical and diagnostic performance needed for the management of the NSTE-ACS patients according to ESC guidelines. A top candidate like the PATHFAST™ cTnI should then be tested in larger and multicentric studies [15].

In conclusion, our strictly controlled study identified the PATHFAST™ cTnI assay as the only one, whose diagnostic performance is comparable to that one of the Abbott hs-cTnI assay used in the central laboratory. Thus, it has the best chance to allow the clinical management of NSTE-ACS patients as safely as fully automated hs-cTn assays at the benefit of shortened turn-around time.

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